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Abstract: BACKGROUND: The use of alkylating chemotherapy versus bevacizumab for recurrent glioblastoma remains controversial. Here, we tested the hypothesis that the activity of alkylators, but not that of bevacizumab, would be associated with the O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status. METHODS: We analyzed a cohort of patients treated at centers of the German Glioma Network or the University Hospital Zurich with alkylating agent-based chemotherapy (n = 260) or bevacizumab without or with irinotecan (n = 84) for first recurrence of glioblastoma. Outcome was stratified for O6-methylguanine DNA methyltransferase (MGMT) status and crossover to bevacizumab or alkylators at further progression. RESULTS: Median post-recurrence survival-1 (PRS-1) for patients receiving alkylating agents at first recurrence was longer than with bevacizumab (11.1 versus 7.4 months, $p < 0.001$). The use of alkylators was associated with longer PRS-1 for patients with a methylated versus unmethylated MGMT promoter ($p = 0.017$). For patients receiving bevacizumab, PRS-1 was not different with or without MGMT promoter methylation. PRS-1 was longer in patients receiving alkylating chemotherapy compared to bevacizumab for patients with methylated ($p < 0.001$) or unmethylated MGMT promoter ($p = 0.034$). For patients with alkylators at first recurrence receiving bevacizumab at any further recurrence, PRS-1 was longer than in patients receiving bevacizumab first and alkylators thereafter ($p = 0.002$). CONCLUSIONS: This study confirms limited value of bevacizumab in recurrent glioblastoma independent of MGMT status. Alkylating agents have activity in recurrent glioblastoma, especially in the context of MGMT promoter methylation.

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Bevacizumab versus alkylating chemotherapy in recurrent glioblastoma

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Abstract

Background:

The use of alkylating chemotherapy versus bevacizumab for recurrent glioblastoma remains controversial. Here we tested the hypothesis that the activity of alkylators, but not that of bevacizumab, would be associated with the *O^6-methylguanine DNA methyltransferase* (*MGMT*) promoter methylation status.

Methods:

We analyzed a cohort of patients treated at centers of the German Glioma Network or the University Hospital Zurich with alkylating agent-based chemotherapy (n=260) or bevacizumab without or with irinotecan (n=84) for first recurrence of glioblastoma. Outcome was stratified for *O^6-methylguanine DNA methyltransferase* (*MGMT*) status and cross-over to bevacizumab or alkylators at further progression.

Results:

Median post-recurrence survival-1 (PRS-1) for patients receiving alkylating agents at first recurrence was longer than with bevacizumab (11.1 versus 7.4 months, p<0.001). The use of alkylators was associated with longer PRS-1 for patients with a methylated versus unmethylated *MGMT* promoter (p=0.017). For patients receiving bevacizumab, PRS-1 was not different with or without *MGMT* promoter methylation. PRS-1 was longer in patients receiving alkylating chemotherapy compared to bevacizumab for patients with methylated (p<0.001) or unmethylated *MGMT* promoter (p=0.034). For patients with alkylators at first recurrence receiving bevacizumab at any further recurrence, PRS-1 was longer than in patients receiving bevacizumab first and alkylators thereafter (p=0.002).

Conclusions:

This study confirms limited value of bevacizumab in recurrent glioblastoma independent of *MGMT* status. Alkylating agents have activity in recurrent glioblastoma, especially in the context of *MGMT* promoter methylation.

Introduction

Glioblastoma exhibits a poor prognosis despite multimodal therapy consisting of surgery followed by temozolomide (TMZ)-based radiochemotherapy. The concept of radiotherapy combined with concomitant and maintenance TMZ as the standard of care was introduced 2005 based on a phase III trial of the European Organisation for Research and Treatment of Cancer (EORTC) / National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) (Stupp et al. 2005). In parallel, promoter methylation of the DNA repair gene *O^6-methylguanine DNA methyltransferase* (*MGMT*) was established as a predictive biomarker for benefit from chemotherapy with TMZ (Hegi et al. 2005). In the pre-TMZ era, population-based overall survival (OS) was 4.9 months (1980-1994) in one study (Ohgaki et al. 2004), and 8.1 months (2000-2003) in another study (Johnson and O'Neill 2012). After the introduction of TMZ in 2005, OS was 9.7 months for the period of 2005 to 2008 in a US study (Johnson and O'Neill 2012) and 11 months between 2005 and 2009 in the Canton of Zurich, Switzerland (Gramatzki et al. 2016). This might be explained at least in part by the increasing use of various, albeit modestly effective therapeutic options at recurrence. Alkylating chemotherapy with TMZ or nitrosoureas (e.g. lomustine, carmustine, fotemustine) and bevacizumab are the agents used most frequently in recurrent glioblastoma. The DIRECTOR trial which compared two different dose-intense TMZ schedules at first recurrence indicated that benefit of TMZ may be restricted to patients with tumors with *MGMT* promoter methylation (Weller et al. 2015).

Bevacizumab was conditionally approved in 2009 in the US and in several other countries based on promising radiographic response rates in 2 phase II trials in patients with recurrent glioblastoma (Friedman et al. 2009; Kreisl et al. 2009). The BELOB phase II trial randomized patients to either bevacizumab or lomustine monotherapy or the combination of both (Taal et al. 2014). Median OS in both monotherapy arms was 8 months, but 12 months for the combination. Yet, an OS benefit for the combination compared to lomustine monotherapy was not confirmed in the ensuing EORTC 26101 phase III trial (Wick et al. 2017). Yet, given the poor performance of dose-dense TMZ in the DIRECTOR trial in patients with *MGMT* promoter-unmethylated tumors (Weller et al. 2015), we hypothesized that bevacizumab might be a preferable option specifically in this cohort of patients with recurrent glioblastoma. The aim of the current study was thus to evaluate the outcome of patients with glioblastoma who received either alkylating agents (TMZ or nitrosoureas) or bevacizumab at first recurrence with respect to *MGMT* promoter methylation status and further treatment at second or later recurrences.

Patients and methods

Patients

We reviewed clinical data of patients who received the alkylating agents TMZ or a nitrosourea-based regimen (lomustine, carmustine or nimustine) as monotherapy or in combination with other chemotherapeutic agents including procarbazine, procarbazine plus vincristine, teniposide, etoposide or blinded cediranib/placebo) or bevacizumab for first recurrence of glioblastoma and who had information on the *MGMT* promoter methylation status of the initial tumor available. Patients treated with a combination of bevacizumab and irinotecan at first recurrence were included but patients who received bevacizumab with any other combination therapy were excluded, including patients who received a combination of alkylators and bevacizumab. The patient cohort consisted of patients treated at centers of the German Glioma Network (GGN), a prospective noninterventional cohort involving eight clinical centers in Germany (www.gliomnetzwerk.de) and of patients, retrospectively analyzed, treated at the University Hospital Zurich, Switzerland. Data for a subset of 41 patients treated at the University Hospital Zurich have been included in a previous publication (Gramatzki et al. 2018). This study was approved by the responsible review committees of the participating centers of the German Glioma Network in Germany (353/2003V) and the University Hospital Zurich, Switzerland (2015-0437). There was no central radiological review for tumor progression. Depending of the respective time of progression either Macdonald criteria (Macdonald et al. 1990) (before 2010) or RANO criteria (Wen et al. 2010) (after their publication in 2010) were applied locally at the sites. The methylation status of the *MGMT* promoter was assessed according to local standards using either methylation-specific PCR or pyrosequencing. Isocitrate dehydrogenase (IDH)1 or IDH2 mutation status was tested by local standards; it was available for 243 patients: 74 tumors were evaluated by immunohistochemistry for $IDH1^{R132H}$, 154 tumors by *IDH1/2* sequencing and 3 tumors by 450K DNA methylation profiling. For 12 patients the method could not be specified during the clinical chart review. Progression-free survival after initial diagnosis of glioblastoma (PFS-1) was calculated from primary surgery to tumor progression, and OS from primary surgery to death or last follow-up. PFS-2 was calculated for the subgroup of patients receiving systemic therapy for second recurrence and defined as the period from the first day of systemic treatment for first recurrence to the date of initiation of any therapeutic intervention for second recurrence. Post-recurrence survival-1 (PRS-1) was calculated from the first day of systemic treatment for recurrent disease to death or the date of last contact. PRS-2 was calculated in the subgroup of patients receiving systemic treatment for second recurrence from the first day of medical treatment for second relapse to death or the date of last contact. Patients were censored at last follow-up. Patient age data are described by median and range. For categorical data absolute and relative frequencies are given. Patient characteristics for groups A versus B were compared by Chi-square-test, Fisher's Exact test and Student's t-test. Survival data were analyzed by log-rank-test and are presented as Kaplan-Meier curves. Cox regression analyses were used to

assess the association of chemotherapy with PRS-1 adjusted for age, first-line therapy, extent of initial surgery and *MGMT* status. All analyses were performed by IBM SPSS Statistics version 25.

Results

Patient characteristics

We identified a total of 344 patients treated either with alkylating chemotherapy (Group A, n=260 total, n=168 with TMZ, n=92 with a nitrosourea-based regimen as specified in Table 1) or bevacizumab (Group B, n=84 total, n=66 with bevacizumab alone, n=18 for bevacizumab in combination with irinotecan) for the first recurrence of glioblastoma. Details on demographic and clinical characteristics are summarized in Table 1. Age, gender, differences in first-line therapy and extent of surgery at first recurrence were well balanced between both groups while significant differences were seen regarding the extent of initial surgery (p=0.006), PFS-1 (p<0.001), Karnofsky performance status (KPS) (p=0.007), *MGMT* promoter methylation status (p<0.001) and IDH mutation status (p=0.006). In group A, 138 patients (53.1%), in group B, 20 patients (23.8%) had tumors with *MGMT* promoter methylation. IDH testing was available for 192 patients (74%) in group A: it was mutant in 23 of these patients (12%). In group B, for 51 patients (61%) IDH testing was available which was uniformly wild-type. To account for this imbalance in patient characteristics, we performed separate analyses of the cohort of patients with known IDH status and excluded patients with IDH-mutant tumors (Table S1).

Outcome

Three hundred seven of 344 patients of the entire cohort died. Median follow-up of surviving patients was 22.1 months. PRS-1 was longer for patients receiving alkylating agent chemotherapy than for patients receiving bevacizumab (Fig. 1A, p<0.001). This was similar for the subgroup of patients with known IDH status and exclusion of patients with IDH-mutant tumors (Fig. 1B, p=0.001). Surgery for recurrence was not prognostic for PRS-1 (HR=0.95, p=0.698). We noted that there were differences in prognostic factors between both cohorts (Table 1) likely related to physicians` choices of the first salvage therapy. PFS-1 had been longer for patients placed on alkylating agents at first recurrence compared to bevacizumab (Fig. 1C for the entire cohort, Fig. 1D for the subgroup of patients with known IDH status and exclusion of patients with IDH-mutant tumors), as was OS from initial diagnosis in these cohorts (p<0.001) (Fig. 1E,F). Median PFS-1 was 8.7 months (95% CI 6.9-10.5) and PRS-1 was 11.1 months (95% CI 10.2-12.1) for patients receiving alkylating agent chemotherapy at first recurrence as opposed to 6.1 months (95% CI 5.2-7.1) and 7.4 (95% CI 5.7-9.0) for patients treated with bevacizumab (Fig. 1G). For the subgroup of patients with known IDH status and exclusion of patients with IDH-mutant tumors, median PFS-1 was 8.7 months (95% CI 6.3-11.1) and median PRS-

1 was 11.1 months (95% CI 9.9-12.3) for patients receiving alkylating agent chemotherapy as opposed to 6.9 months (95% CI 5.3-8.5) and 7.1 months (95% CI 5.2-9.1) for patients receiving bevacizumab at first recurrence (Fig. 1H). We performed subgroup analyses for the patients receiving alkylating agents regarding differences in PFS-1 or OS when stratified by use of TMZ or nitrosoureas. Both PFS-1 and OS were longer for patients receiving TMZ versus nitrosoureas for first recurrence ($p=0.003$ and $p=0.04$) for the entire patient cohort. For the subcohort of patients with known IDH status and after exclusion of patients with IDH-mutant tumors, PFS-1 was still longer for patients receiving TMZ versus nitrosoureas ($p=0.005$) while no difference was seen for OS ($p=0.164$).

MGMT promoter methylation status and outcome

Next, we stratified the patient cohorts with respect to *MGMT* promoter methylation status. PRS-1 for patients receiving alkylating agent chemotherapy at first recurrence was longer for patients with *MGMT* promoter-methylated tumors than for unmethylated tumors (Fig. 2A, $p=0.017$). For the patients receiving bevacizumab, PRS-1 was not different by *MGMT* promoter methylation status. PRS-1 was longer in the group receiving alkylating chemotherapy than in the group with bevacizumab both for patients with tumors with methylated or with unmethylated *MGMT* promoter ($p<0.001$ and $p=0.034$). For the subgroup of patients with known IDH status and exclusion of patients with IDH-mutant tumors, there was only a trend towards a PRS-1 difference for patients receiving alkylating chemotherapy with methylated versus unmethylated *MGMT* promoter (Fig. 2B, $p=0.15$). For the comparison of patients receiving alkylating chemotherapy versus bevacizumab, longer PRS-1 was only seen in patients with *MGMT* promoter-methylated tumors ($p<0.001$), while there was no difference if difference in patients with *MGMT* promoter-unmethylated tumors ($p=0.12$) (Fig. 2B). As above, we also looked at the overall disease trajectory in these patient groups. PFS-1 and OS were longer in patients receiving alkylating agents versus bevacizumab at first progression both in case of a methylated *MGMT* promoter ($p=0.004$ and $p<0.001$) and in case of an unmethylated *MGMT* promoter ($p=0.014$ and $p=0.001$) (Fig. 2C,E). For the subgroup excluding patients with IDH-mutant tumors, there was no significant difference for PFS-1 both with and without *MGMT* promoter methylation ($p=0.11$ and $p=0.14$), while OS was longer both with and without *MGMT* promoter methylation ($p<0.001$ and $p=0.026$) for patients receiving alkylators than for patients receiving bevacizumab (Fig. 2D,F). Patients receiving alkylating agents at first progression had longer PFS-1 and OS when their tumors carried a methylated *MGMT* promoter ($p<0.001$ and $p<0.001$ for the entire patient cohort, Fig. 2C,E; $p<0.001$ and $p=0.001$ for the subgroup with known IDH status and after exclusion of patients with IDH-mutant tumors, Fig. 2D,F). Median PFS-1 in the patient group treated with alkylating agents was 15.0 months (95% CI 11.0-18.9) for patients with *MGMT* promoter-methylated tumors and 6.5 months (95% CI 5.5-7.4) for patients with *MGMT* promoter-unmethylated tumors, as well as 8.7 months (95% CI 7.6-9.9) and 5.6 months (95%

CI 5.0-6.3) for patients receiving bevacizumab stratified according to methylated and unmethylated *MGMT* promoter status. Median PRS-1 in the group treated with alkylating agents was 12.2 months (95% CI 10.1-14.3) for *MGMT* promoter-methylated and 8.7 months (95% CI 7.0-10.3) for *MGMT* promoter-unmethylated glioblastoma patients, and in the group receiving bevacizumab 8.2 months (95% CI 3.8-12.6, *MGMT* promoter methylated) and 7.3 months (95% CI 6.0-8.7, *MGMT* promoter unmethylated), respectively (Fig. 2G). Median PFS-1 and median PRS-1 with stratification for *MGMT* status for the subgroup with exclusion of IDH-mutant tumors are shown in Fig. 2H.

Further salvage therapies and outcome

Differences in PRS may also depend on subsequent salvage therapies. Details regarding the different salvage therapies for second or later recurrences are shown in Table S2. PRS-1 for patients with alkylating chemotherapy at first recurrence who received bevacizumab at any further recurrence was longer than for patients receiving bevacizumab at first recurrence and alkylating chemotherapy salvage therapy at any further progression (Fig. 3A for the entire cohort, $p=0.002$, Fig. 3B for the subgroup with known IDH status and excluding IDH-mutant tumors, $p<0.001$). PRS-1 for patients that received alkylating chemotherapy at first recurrence and no bevacizumab at any further recurrence was longer than in patients receiving bevacizumab at first recurrence and no alkylating chemotherapy as salvage therapy at any further progression (Fig. 3A for the entire cohort, $p<0.001$, Fig. 3B for the subgroup excluding IDH-mutant tumors, $p=0.001$). PFS-1 and OS stratified for differences in further salvage therapy were significantly longer when comparing the patient groups receiving alkylating agents at first recurrence followed by a bevacizumab-containing regimen versus those receiving bevacizumab first and alkylating agents thereafter ($p<0.001$ for PFS-1, $p<0.001$ for OS). Further, PFS-1 and OS were longer for patients receiving alkylating agents first and thereafter no bevacizumab versus receiving bevacizumab first and no alkylating agents thereafter ($p<0.001$ for PFS-1, $p<0.001$ for OS) (Fig. 3C,E). For the subgroup of patients with exclusion of patients with IDH-mutant tumors, differences in PFS-1 and OS comparing these patient groups were similar, with the exception that there was no significant difference in PFS-1 when comparing patients receiving alkylating agents first and no bevacizumab thereafter with patients receiving bevacizumab first and no alkylating agents thereafter ($p=0.055$) (Fig. 3D,F). Median PFS-1 and median PRS-1 are shown in Fig. 3G for the entire patient cohort and Fig. 3H for the subgroup excluding IDH-mutant tumors, 95%-confidence intervals for these outcome parameters are summarized in Table S3. For those patients receiving further systemic salvage therapy for second recurrence (n=183 for the entire cohort and n=113 for the cohort with known IDH status and exclusion of patients with IDH-mutant tumors), we assessed the median time from initiation of systemic treatment for first recurrence until the initiation of any salvage therapy for second recurrence (“PFS-2”) and survival from initiation of systemic treatment for second

recurrence to death or the date of last contact ("PRS-2") (Fig. 3 IJ). Statistical analyses were omitted for the patient group with bevacizumab at first recurrence receiving any other systemic salvage therapy but no alkylators at second recurrence due to low patient numbers (n=5 for the entire cohort and n=2 for the subgroup with exclusion of patients with IDH-mutant tumors). There was no difference in PFS-2 but longer PRS-1 (p=0.002) and PRS-2 (p<0.001) when comparing patients receiving alkylating chemotherapy first and a bevacizumab-containing regimen thereafter (n=74) versus bevacizumab first and alkylators thereafter (n=39). PFS-2 was shorter (p=0.033) while PRS-1 and PRS-2 were not different for patients with alkylating agents first and bevacizumab for second or later salvage therapy versus any other salvage therapy but no bevacizumab (n=65). For the subgroup with known IDH status and exclusion of patients with IDH-mutant tumors, similarly, PFS-2 was not different, PRS-1 (p<0.001) and PRS-2 (p<0.001) were longer when comparing patients receiving alkylating chemotherapy first and a bevacizumab-containing regimen thereafter (n=46) versus bevacizumab first and alkylators thereafter (n=26). In this subcohort, PFS-2, PRS-1 and PRS-2 were not different for patients with alkylating agents first and bevacizumab thereafter versus any other salvage therapy but no bevacizumab for second or later salvage therapy (n=39).

Multivariate analyses

We performed multivariate Cox regression analyses (Table 2) to account for differences in potential prognostic factors for PRS-1 in patients treated with alkylating agents versus bevacizumab-containing regimens at first recurrence. We started with a model including all patients with available documentation (n=317) on age, *MGMT* promoter methylation, first-line therapy and extent of initial surgical resection (model 1). PRS-1 was superior in patients receiving alkylating agents versus bevacizumab for first recurrence (hazard ratio (HR)=0.59, 95% CI 0.44-0.78, p<0.001). Age and *MGMT* promoter methylation had significant prognostic relevance. KPS as a known prognostic factor for newly diagnosed glioblastoma was omitted for this analysis since no prognostic role was determined in the DIRECTOR trial evaluating two different regimens of TMZ for recurrent glioblastoma (Weller et al. 2015) and data for KPS at recurrence were only available for a subset of patients (229 of 317). Next, we analyzed a Cox regression model for PRS-1 comparing patients with alkylating chemotherapy at first recurrence receiving bevacizumab thereafter versus bevacizumab first and alkylating agents at any further recurrence as well as comparing the group with alkylating agents first and no bevacizumab at further recurrence versus bevacizumab first and no alkylators thereafter (model 2). In this model, the difference in PRS-1 in patients receiving alkylating agents at first recurrence and bevacizumab thereafter compared to patients with bevacizumab first and alkylating agents thereafter was not significant (HR=0.66, 95% CI 0.42-1.02, p=0.063). Furthermore, this model confirmed superior PRS-1 in patients with alkylators first and no bevacizumab at further recurrence

compared to bevacizumab first and no alkylators thereafter (HR=0.46, 95% CI 0.32-0.66, p<0.001). Similar to model 1, *MGMT* promoter methylation and age were of significant prognostic relevance for PRS-1. We also performed the multivariate analyses of models 1 and 2 for the subcohort of patients with known IDH status and exclusion of patients with IDH-mutant tumors (Table S4, n=206). In model 1, prognostic significance for PRS-1 for patients receiving alkylating agents versus bevacizumab at first recurrence was confirmed with a HR of 0.57 (95% CI 0.39-0.83, p=0.003) while *MGMT* status and age were not prognostic. In model 2, PRS-1 was superior for patients receiving alkylating agents at first recurrence both for the comparison of alkylators first and bevacizumab at any further recurrence with bevacizumab first and alkylating agents thereafter (HR=0.54, 95% CI 0.31-0.94, p=0.03) and for the comparison of alkylating agents first and no bevacizumab at further recurrence with bevacizumab first and no alkylators thereafter (HR=0.48, 95% CI 0.30-0.77, p=0.003). Comparable to model 1 for this subcohort, *MGMT* status and age were not significant prognostic co-factors.

Discussion

This study explored the outcome of patients with glioblastoma treated with either alkylating chemotherapy or bevacizumab at first recurrence, stratified for *MGMT* promoter methylation status and further salvage treatment. Worldwide, there is no consensus for standard of care for patients with glioblastoma at first recurrence. With respect to medical therapy, bevacizumab is approved for treatment of recurrent glioblastoma in the US and some other countries, but not in the European Union. In Europe, treatment with alkylating agents is a widely accepted regimen for patients with recurrent glioblastoma (Weller et al. 2017) not only, but also because the access to bevacizumab is limited. Accordingly, lomustine was chosen as a comparator for experimental agents in several randomized phase III trials (Batchelor et al. 2013; Wick et al. 2017; Wick et al. 2010). The choice of either alkylating chemotherapy or bevacizumab for treatment at recurrence of glioblastoma may also depend on *MGMT* promoter methylation status since the DIRECTOR trial showed a much more favorable outcome of patients with *MGMT* promoter-methylated tumors treated with TMZ compared to patients with *MGMT* promoter-unmethylated tumors (Weller et al. 2015). Although the EORTC 26101 phase III trial showed no OS benefit for the combination of bevacizumab and lomustine versus lomustine alone (Wick et al. 2017), the prolongation of progression-free survival with bevacizumab may be considered beneficial, especially in the context of a tumor-related symptom burden. In summary, the question of whether alkylating chemotherapy or bevacizumab should be the preferred treatment option at first recurrence remains controversial.

Our analysis supports the choice of alkylating chemotherapy at first recurrence and postponing treatment with bevacizumab since PRS-1 was longer for patients receiving alkylating chemotherapy

compared with bevacizumab at first recurrence (Fig. 1A,B), with a HR of 0.59 in multivariate analysis (Table 2). We acknowledge that differences in prognostic factors may contribute to the reported outcome data since *MGMT* promoter methylation and age were significant prognostic cofactors for PRS-1 on multivariate analysis (Table 2).

Notably, PRS-1 of patients receiving alkylating chemotherapy was longer than in patients receiving bevacizumab independent of the *MGMT* promoter methylation status (Fig. 2). Given the poor outcome for patients with *MGMT* promoter-unmethylated tumors and the lack of a difference in PRS-1 between the patient groups receiving either bevacizumab or alkylating agents in the subcohort with known IDH-status and exclusion of patients with IDH-mutant tumors, the use of any salvage therapy in patients with an *MGMT* promoter-unmethylated glioblastoma is questionable. So far, there are no data comparing alkylating agents or bevacizumab versus best supportive care especially in the group of patients with *MGMT* promoter-unmethylated glioblastoma. Data of the BELOB phase II trial, suggested longer OS in patients with recurrent glioblastoma with *MGMT* promoter methylation receiving bevacizumab rather than lomustine (Taal et al. 2014). However, this was not confirmed in the EORTC 26101 phase III trial showing a prognostic role of *MGMT* promoter methylation independent of whether patients were treated with lomustine plus bevacizumab or bevacizumab alone (Wick et al. 2017). Conclusions regarding the value of *MGMT* status and the efficacy of lomustine, however, are limited since there is no lomustine-free treatment arm in this trial. In summary, we conclude that the use of bevacizumab is not supported by presence versus absence of *MGMT* promoter methylation while the use of alkylating chemotherapy may be beneficial in patients with recurrent glioblastoma and a methylated *MGMT* promoter.

Regarding the role of further salvage therapy after treatment with either alkylating agents or bevacizumab for first recurrence, we found longer PRS-1 and PRS-2-when alkylators were used first and bevacizumab thereafter in contrast to the use of bevacizumab first and alkylating agents thereafter (Fig. 3). We acknowledge that interpretation of these data is limited by potential selection bias of the treating physicians, differences in prognostic factors and heterogeneity of salvage therapies including the fact that patients were grouped for receiving alkylators or bevacizumab at any further recurrence without further stratification for the number of recurrences which would have further limited sample sizes of the respective subgroups. However, the more favorable outcome for patients receiving alkylators versus bevacizumab for first recurrence was confirmed on multivariate analyses with *MGMT* promoter methylation and age as prognostic cofactors (Table 2 and S4, model 1). Still, in the multivariate analyses regarding the different crossover regimens, PRS-1 was superior for the group of patients with alkylators first and a bevacizumab-containing regimen thereafter compared with bevacizumab first and alkylators thereafter was only confirmed for the subgroup with known IDH-

status and exclusion of IDH-mutant patients and not for the entire patient cohort (Table 2 and S4, model 2).

The observation that the early use of bevacizumab for recurrent glioblastoma might not be beneficial is supported by an epidemiologic study showing that PRS of patients receiving no bevacizumab at first recurrence was longer than in patients that received the drug as first choice for recurrent disease (Gramatzki et al. 2018). A retrospective series of 298 patients with recurrent glioblastoma did not find significant differences for the median time to further tumor progression after initiation of bevacizumab between patients with early versus delayed administration of bevacizumab while median OS was longer in patients with delayed administration of bevacizumab (Hamza et al. 2014). The benefit in OS in the latter study may be interpreted by selection bias and prognostic factors but also may point towards a benefit of other therapies including alkylators applied early for recurrent glioblastoma. Another retrospective study with 468 patients receiving bevacizumab for different recurrences of glioblastoma similarly did not find significant differences, neither with regard to the time to further tumor progression nor to the survival time after initiation of bevacizumab (Piccioni et al. 2014). The EORTC 26101 trial had initially started as a phase II trial including treatment arms of bevacizumab and lomustine monotherapy with the possibility of crossover at further recurrence. The results of the early phase of this trial as published at ASCO 2016 indicated similar median OS for the different treatment groups (Wick et al. 2016). However, the final results may add further evidence to decide on the sequence of either alkylating chemotherapy or bevacizumab in treatment of recurrent glioblastoma.

Given the poor outcome for patients treated with bevacizumab in our cohort and in the studies discussed above (Gramatzki et al. 2018; Hamza et al. 2014; Wick et al. 2017), its use for patients with recurrent glioblastoma remains questionable. Symptom control remains one of the main indications. In the context of reirradiation, reduced radiation-associated toxicity has been reported with regard to symptomatic radionecrosis and symptomatic edema when patients are co-exposed to bevacizumab (Fleischmann et al. 2019). However, the value of reirradiation alone or in combination bevacizumab for patients with recurrent glioblastoma remains controversial due to the lack of prospective randomized studies. One retrospective study with 71 patients indicated some potential benefit for PFS and OS (Flieger et al. 2014) while another retrospective analysis of a small cohort with 14 patients reported higher PFS but shorter OS for patients with recurrent “high-grade” glioma treated by reirradiation with and without bevacizumab (Hundsberger et al. 2013). Prospective evaluation of combined reirradiation and bevacizumab was done in a phase-1 trial with a total of 15 patients with a dose escalation up to 3x11 Gy reporting a median overall survival of 13 months (Clarke et al. 2017).

Beyond the limitations of our study that have already been discussed, we also acknowledge that the retrospective character of analysis limits data interpretation also with regard to the heterogeneity of patient cohorts and small patient numbers in subgroups.

In conclusion, this study confirms that the value of bevacizumab in recurrent glioblastoma is limited with regard to survival and that outcome is independent of the *MGMT* status. Alkylating agents such as TMZ and lomustine have activity in patients with recurrent glioblastoma, mainly in the context of a methylated *MGMT* promoter.

Figure legends:

Fig. 1. Outcome stratified for treatment at first recurrence. Outcome for the entire patient cohort (left) or the subgroup of patients with known IDH status and exclusion of patients with IDH-mutant tumors (right) treated with alkylating agents (blue curve) or bevacizumab alone or in combination with irinotecan (red curve) at first recurrence: Post-recurrence survival-1 (PRS-1) (A,B), progression-free survival from initial diagnosis (PFS-1) (C,D), overall survival (OS) from initial diagnosis (E, F), and median PFS-1 and median PRS-1 (G,H)

Fig. 2. Outcome stratified by treatment and *MGMT* status. Outcome data for the entire patient cohort (left) or the subgroup of patients with known IDH status and exclusion of patients with IDH-mutant tumors (right) treated at first recurrence with either alkylating agents (blue curves) or bevacizumab (red curves) stratified for methylated (continuous line) or unmethylated (dashed line) *MGMT* promoter: post-recurrence survival-1 (PRS-1) (A,B), progression-free survival from initial diagnosis (PFS-1) (C,D), overall survival (OS) from initial diagnosis (E,F), and median PFS-1 and median PRS-1 (G,H).

Fig. 3. Outcome stratified for further salvage therapies. Outcome data for the entire patient cohort (left) or the subgroup of patients with known IDH status and exclusion of patients with IDH-mutant tumors (right) treated at first recurrence with alkylating agents followed by a bevacizumab-containing regimen at any further recurrence (blue continuous line) or never received bevacizumab at any further salvage therapy (blue dashed line) or treated with a bevacizumab-containing regimen at first recurrence followed by treatment with alkylators at any further recurrence (red continuous line) or never receiving alkylators at any further salvage therapy (red dashed curve): post-recurrence survival-1 (PRS-1) (A,B), progression-free survival from initial diagnosis (PFS-1) (C,D), overall survival (OS) from initial diagnosis (E,F), median PFS-1 and median PRS-1 (G,H). In the subgroup of patients receiving further systemic therapy after second recurrence, median PFS-1, median time from initiation of systemic treatment for first recurrence until the initiation of any salvage therapy for second recurrence (PFS-2) and survival from systemic treatment for second recurrence to death (PRS-2) was also assessed (I,J).

Disclosures and declarations:

Ethical approval:

This study was approved by the responsible review committees of the participating centers of the German Glioma Network in Germany (www.gliomnetzwerk.de) (353/2003V) and the University Hospital Zurich, Switzerland (2015-0437). The study was performed in accordance with the Declaration of Helsinki.

Availability of data and material:

The datasets of the study are available from the corresponding author on reasonable request and provided that the request is in line with the regulations of the review committees.

Disclosure of potential conflicts of interest

KS has received honoraria for board participation from Roche. GR has received honoraria from advisory boards from Abbvie. UH reports grants and personal fees from Roche, personal fees and non-financial support from Medac, personal fees and non-financial support from Bristol-Myers Squibb, personal fees from Novocure, personal fees from Novartis, personal fees from Daichii-Sankyo, personal fees from Riemser, personal fees from Noxxon, personal fees from AbbVie, personal fees from Bayer. MiW has received research grants from Abbvie, Adastra, Dracen, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Piqur and Roche, and honoraria for lectures or advisory board participation or consulting from Abbvie, Basilea, Bristol Meyer Squibb (BMS), Celgene, Merck, Sharp & Dohme (MSD), Merck (EMD), Novocure, Orbus, Roche and Tocagen. The other authors report no conflicts of interest.

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Author contributions:

KS, SL, DG, UH, MaW, GS, NT, US, MT, WW contributed patient data, KS, BH and MiW wrote the manuscript, BH performed statistical analyses, GR, FL and TP were involved in molecular analysis of tumors for a subset of patients. MiW designed the project and supervised the study. All authors discussed the results and reviewed the manuscript.

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Table 1: Patient characteristics for the entire cohort

Therapy for first recurrence	**Alkylating agent-based chemotherapy (Group A, n=260)[1]**	**Bevacizumab (Group B, n=84)[2]**	***p* value**
Age at diagnosis (years)			
Median (Range)	58 (24-80)	55 (25-79)	0.341
Gender			
Male	157 (60.4%)	53 (63.1%)	0.658
Female	103 (39.6%)	31 (36.9%)	
Initial surgery			
Gross total resection	115 (48.9%)	23 (28.0%)	0.006
Subtotal resection (50-99%)	80 (34.0%)	34 (41.5%)	
Partial resection (<50%)	24 (10.2%)	14 (17.1%)	
Biopsy	16 (6.8%)	11 (13.4%)	
No data	25	2	
First-line therapy			
Radiotherapy alone	44 (16.9%)	11 (13.1%)	0.517
Radiotherapy plus TMZ	200 (76.9%)	70 (83.3%)	
Radiotherapy plus others[3]	6 (2.3%)	0 (0%)	
Radiotherapy plus TMZ plus others[3]	10 (3.8%)	3 (3.6%)	
PFS-1 (months)			
Median (95% CI)	8.7 (6.9-10.5)	6.1 (5.2-7.1)	<0.001
Karnofsky performance score at recurrence			
90-100	70 (38.5%)	17 (27.4%)	0.007
70-80	86 (47.3%)	25 (40.3%)	
<70	26 (14.3%)	20 (32.3%)	
Not available	78	22	
Surgery at first recurrence	100/260 (38.5%)	13/84 (15.5%)	
Gross total resection	44 (51.8%)	2 (20.0%)	0.183
Subtotal resection (50-99%)	33 (38.8%)	7 (70.0 %)	
Partial resection (<50%)	8 (9.4 %)	1 (10.0%)	
Extent of resection unknown	15	3	

***MGMT* promoter methylation status**			
Methylated	138 (53.1%)	20 (23.8%)	<0.001
Unmethylated	122 (46.9%)	64 (76.2%)	
IDH1/2 mutation status			
Mutated	23 (12.0%)	0 (0%)	0.006
Not mutated	169 (88.0%)	51 (100%)	
Unknown	68	33	

[1]168 patients received TMZ, 92 patients received a nitrosourea-based regimen with monotherapy with lomustine (n=23), carmustine (n=15) or nimustine (n=9), or combination regimens with procarbazine, lomustine and vincristine (n=15), procabazine and lomustine (n=1), nimustine plus teniposide (n=12), carmustine plus teniposide (n=9), lomustine plus etoposide (n=7), lomustine plus cediranib or placebo (blinded, n=1)

[2]18 patients received irinotecan in addition

[3]Other therapies applied were tumor-treating fields, cilengitide, enzastaurin, cetuximab, temsirolimus, galunisertib, proton beam therapy, gene therapy

Table 2: Multivariate analysis for survival after first recurrence (PRS-1)

Model	Factor	HR	95% CI	*p* value
1 (n=317)	Therapy at recurrence: Alkylating agents versus bevacizumab (ref)	0.59	0.44-0.78	<0.001
	MGMT: Methylated versus unmethylated (ref)	0.75	0.59-0.97	0.027
	Age (years) ≤65 versus >65 (ref)	0.66	0.49-0.87	0.004
	Firstline therapy Radiotherapy plus TMZ +/- others versus radiotherapy +/- others (ref)	0.99	0.73-1.36	0.970
	Extent of initial surgery: Gross total versus no total (ref)	0.90	0.71-1.14	0.373
2 (n=317)	Therapy at recurrence: Alkylating agents → bevacizumab versus Bevacizumab → alkylating agents (ref) Alkylating agents → no bevacizumab versus Bevacizumab → no alkylating agents (ref)	0.66 0.46	0.42-1.02 0.32-0.66	0.063 <0.001
	MGMT: Methylated versus unmethylated (ref)	0.73	0.57-0.93	0.013
	Age (years) ≤65 versus >65 (ref)	0.69	0.52-0.91	0.010
	Firstline therapy Radiotherapy plus TMZ +/- others versus radiotherapy +/- others (ref)	0.97	0.71-1.33	0.868
	Extent of initial surgery: Gross total versus no total (ref)	0.88	0.70-1.12	0.306

Table S1: Patient characteristics for the subgroup with known IDH status excluding patients with IDH-mutant tumors

Therapy for first recurrence	**Alkylating agent-based chemotherapy (Group A), n=169**	**Bevacizumab with or without irinotecan (Group B), n=51**	**p-value**
Age at diagnosis (years)			
Median (Range)	58 (29-80)	56 (29-79)	0.490
Gender			
Male	97 (57.4%)	33 (64.7%)	0.352
Female	72 (42.6%)	18 (35.3%)	
Initial surgery			
Gross total resection	80 (51.3%)	15 (30.0%)	0.025
Subtotal resection (50-99%)	55 (35.3%)	21 (42.0%)	
Partial resection (<50%)	12 (7.7%)	8 (16.0%)	
Biopsy	9 (5.8%)	6 (12.0%)	
No data	13	1	
First-line therapy			
Radiotherapy alone	28 (16.6%)	7 (13.7%)	0.927
Radiotherapy plus TMZ	134 (79.3%)	43 (84.3%)	
Radiotherapy plus others[1]	2 (1.2%)	0 (0%)	
Radiotherapy plus TMZ plus others[1]	5 (3.0%)	1 (2.0%)	
PFS-1 (months)			
Median (95% CI)	8.7 (6.3-11.3)	6.9 (5.3-8.5)	<0.001
Karnofsky performance score at recurrence			
90-100	42 (34.4%)	13 (34.2%)	0.014
70-80	65 (53.3%)	13 (34.2%)	
<70	15 (12.3%)	12 (31.6%)	
Not available	47	13	
Surgery at first recurrence	71/169 (42.0%)	8/51 (15.7%)	

Gross total resection	34 (56.7%)	2 (28.6%)	0.254
Subtotal resection (50-99%)	22 (36.7%)	5 (71.4 %)	
Partial resection (<50%)	4 (6.7%)	0 (0.0%)	
Extent of resection unknown	11	1	
***MGMT* promoter methylation status**			
Methylated	88 (52.1%)	11 (21.6%)	<0.001
Unmethylated	81 (47.9%)	40 (78.4%)	

[1]Tumor-treating fields, cilengitide, temsirolimus, galunisertib, proton beam therapy, gene therapy

Table S2: Details on therapeutic regimens at second or later recurrence

Therapy for first recurrence	**Alkylating agents (n=260)**		**Bevacizumab (n=84)**	
Salvage therapy at second or later recurrence	**Bevacizumab/ bevacizumab-containing regimen (total n=74)**	**No bevacizumab (total n=186)**	**Alkylating agent-based chemotherapy (total n=39)**	**No alkylating agents (total n=45)**
- patients without any systemic therapy for second or later recurrence	n=0	n=121	n=0	n=40
- patients with *at least* 1 further line of salvage therapy	n= 74	n=65	n= 39	n=5
Bevacizumab				
- alone	n=55[1]	n=0	n=0	n=2
- plus irinotecan	n=19[1]	n=0	n=1	n=0
- plus doxorubicin	n=0	n=0	n=0	n=1
Nitrosourea/nitrosourea-based regimen[2]	n=21[3]	n=31	n=35[4]	
Temozolomide	n=6	n=28	n=4	
Hydroxyurea + Imatinib		n=8		
Temsirolimus	n=3			
Irinotecan		n=1		
Etoposide			n=1	n=1
Hydroxyurea		n=1		
Imatinib		n=2		

Trophosphamide + etoposide		n=1		
APG101			n=1	
Ifosfamide + carboplatin + etoposide	n=2			
Carboplatin	n=1		n=1	
Carboplatin + etoposide				n=1
Parvovirus-based therapy	n=1			
BGJ398			n=1	
Everolimus			n=1	
Erlotinib + Sirolimus		n=1		
Teniposide		n=1		
Cilengitide			n=1	
Nivolumab	n=1			
Radioimmunotherapy (not otherwise specified)		n=1		
Re-irradiation applied as salvage therapy at any further recurrence	14	22	4	1

[1]One patient received bevacizumab monotherapy followed by bevacizumab in combination with irinotecan

[2]This group includes regimens with nitrosoureas alone as well as nitrosoureas in combination with various other chemotherapies (procarbazine, procarbazine+vincristine, teniposide, irinotecan, etoposide, enzastaurin, cytarabin)

[3]One of these patients with a nitrosourea-based regimen received bevacizumab in combination with nitrosoureas

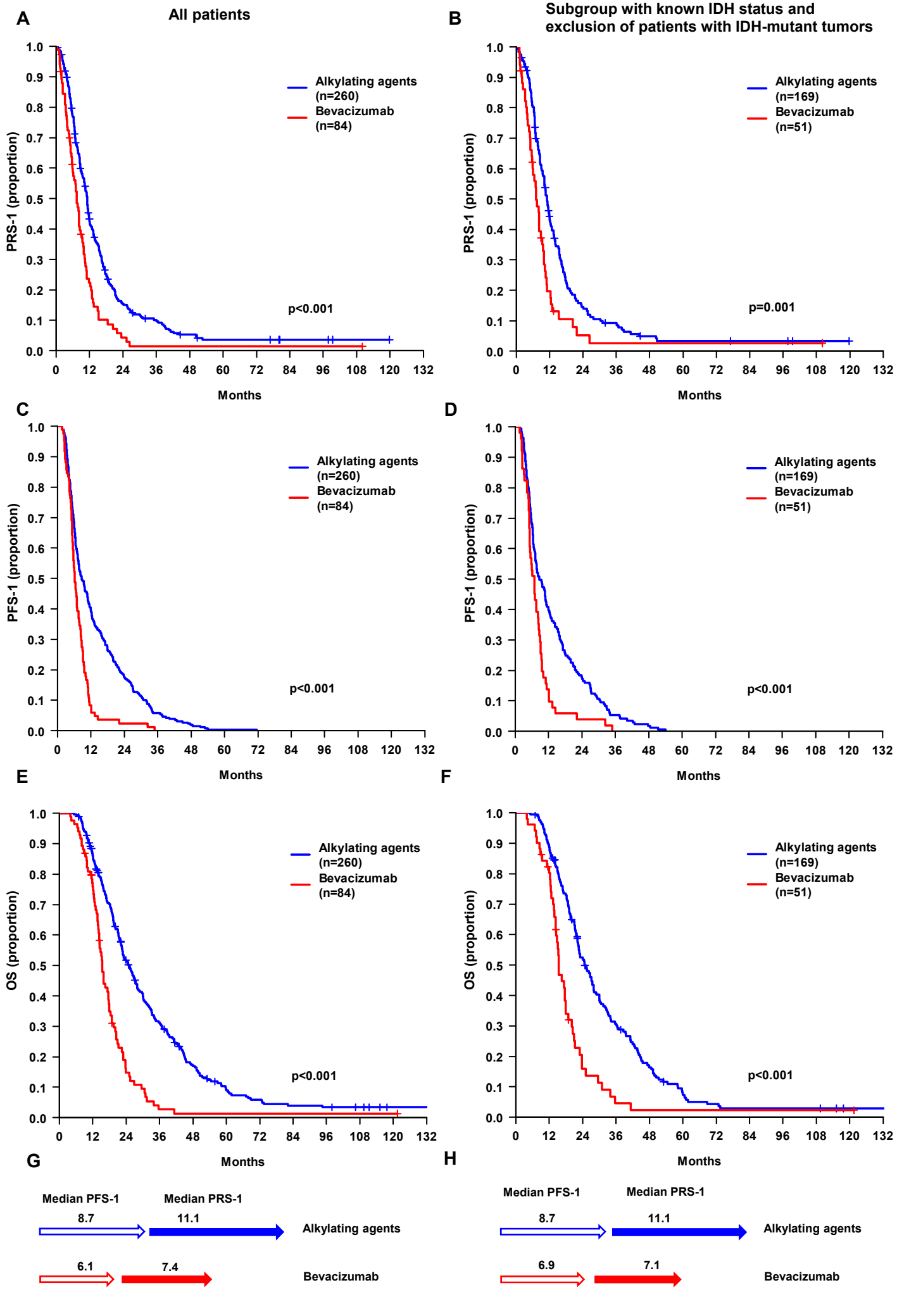
[4]This group also includes patients with continuation of bevacizumab used in combination with a nitrosourea-based regimen for second or later recurrence

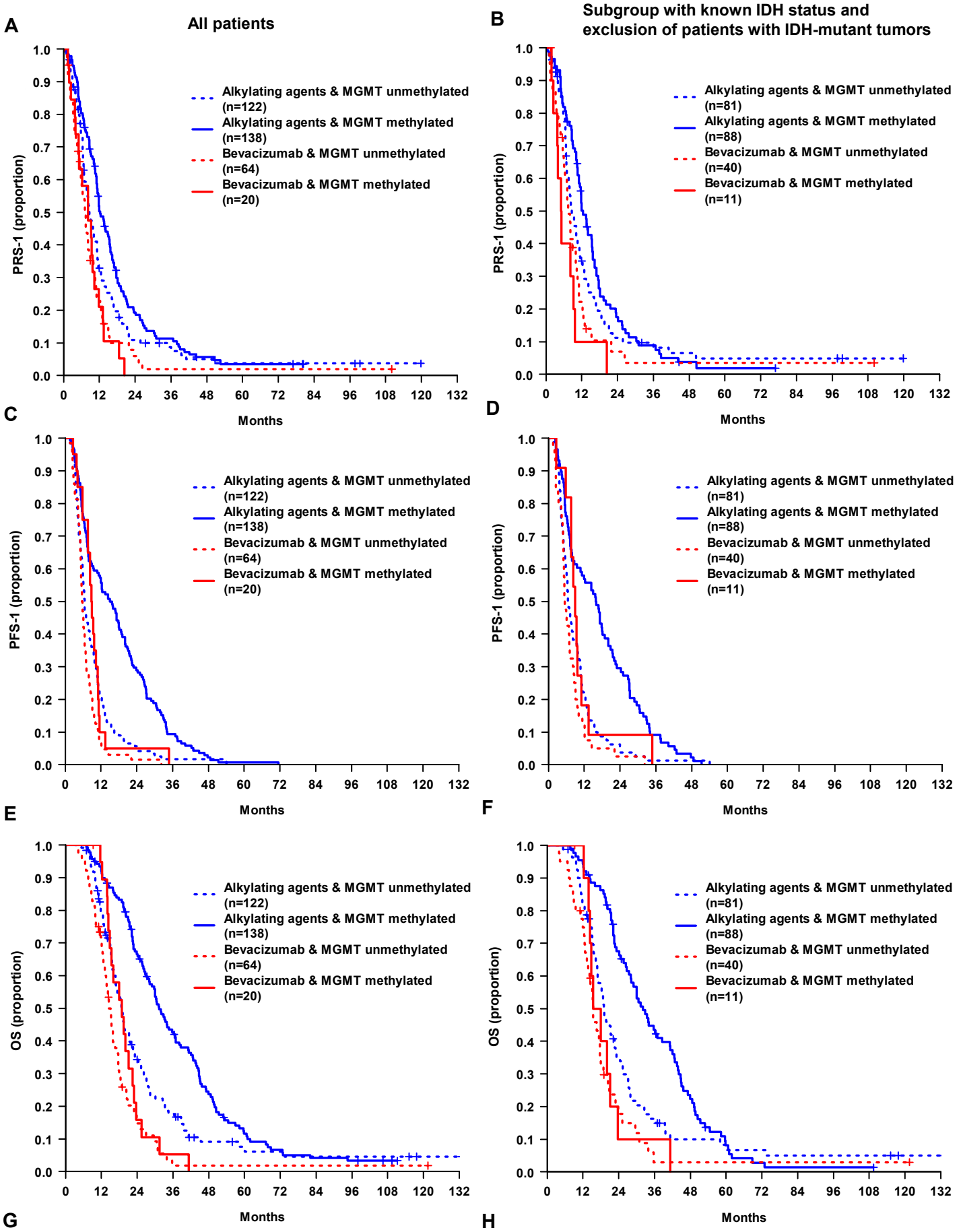
Table S3: Outcome stratified for further salvage therapies

	All patients n=344				**Patient cohort with known IDH status and exclusion of patients with IDH-mutant-tumors n=220**			
Therapy at first recurrence	Alkylating agents, n=260		Bevacizumab, n=84		Alkylating agents, n=169		Bevacizumab, n=51	
Salvage therapy at any further recurrence	Bevacizumab/ bevacizumab-containing regimen, n=74	No bevacizumab n=186	Alkylating agents, n=39	No alkylating agents, n=45	Bevacizumab/ bevacizumab-containing regimen, n=46	No bevacizumab n=123	Alkylating agents, n=26	No alkylating agents, n=25
Median PFS-1 (95%-CI)	9.4 months (6.7-12.2)	8.3 months (6.0-10.6)	6.0 months (4.4-7.6)	6.2 months (5.2-7.2)	10.5 months (5.9-15.1)	7.8 months (5.6-10.1)	5.5 months (3.5-7.5)	7.1 months (4.9-9.4)
Median PRS-1 (95%-CI)	14.1 months (11.1-17.2)	9.4 months (7.7-11.2)	9.9 months (8.7-11.1)	5.1 months (3.5-6.7)	15.5 months (13.1-17.8)	9.4 months (7.8-11.1)	9.7 months (8.2-11.3)	4.6 months (2..8-6.3)

Table S4: Multivariate analysis for survival after first recurrence in the subgroup of patients with known IDH status and exclusion of patients with IDH-mutant-tumors

Model	Factor	HR	95% CI	*p* value
1 (n=206)	Therapy at recurrence: Alkylating agents versus bevacizumab (ref)	0.57	0.39-0.83	0.003
	MGMT: Methylated versus unmethylated (ref)	0.86	0.62-1.18	0.339
	Age (years) ≤65 versus >65 (ref)	0.81	0.56-1.17	0.264
	Firstline therapy Radiotherapy plus TMZ +/- others versus radiotherapy +/- others (ref)	0.87	0.56-1.33	0.504
	Extent of initial surgery: Gross total versus no total (ref)	0.80	0.60-1.07	0.132
2 (n=206)	Therapy at recurrence: Alkylating agents → bevacizumab versus Bevacizumab → alkylating agents (ref) Alkylating agents → no bevacizumab versus Bevacizumab → no alkylating agents (ref)	0.54 0.48	0.31-0.94 0.30-0.77	0.03 0.003
	MGMT: Methylated versus unmethylated (ref)	0.86	0.63-1.19	0.373
	Age (years) ≤65 versus >65 (ref)	0.86	0.60-1.25	0.435
	Firstline therapy Radiotherapy plus TMZ +/- others versus radiotherapy +/- others (ref)	0.81	0.53-1.23	0.321
	Extent of initial surgery: Total versus no total (ref)	0.80	0.60-1.07	0.134


A
All patients
PRS-1 (proportion)
Alkylating agents (n=260)
Bevacizumab (n=84)
p<0.001
Months
B
Subgroup with known IDH status and exclusion of patients with IDH-mutant tumors
PRS-1 (proportion)
Alkylating agents (n=169)
Bevacizumab (n=51)
p=0.001
Months
C
PFS-1 (proportion)
Alkylating agents (n=260)
Bevacizumab (n=84)
p<0.001
Months
D
PFS-1 (proportion)
Alkylating agents (n=169)
Bevacizumab (n=51)
p<0.001
Months
E
OS (proportion)
Alkylating agents (n=260)
Bevacizumab (n=84)
p<0.001
Months
F
OS (proportion)
Alkylating agents (n=169)
Bevacizumab (n=51)
p<0.001
Months
G
Median PFS-1
Median PRS-1
8.7
11.1
Alkylating agents
6.1
7.4
Bevacizumab
H
Median PFS-1
Median PRS-1
8.7
11.1
Alkylating agents
6.9
7.1
Bevacizumab


A
All patients
PRS-1 (proportion)
Months
Alkylating agents & MGMT unmethylated (n=122)
Alkylating agents & MGMT methylated (n=138)
Bevacizumab & MGMT unmethylated (n=64)
Bevacizumab & MGMT methylated (n=20)
B
Subgroup with known IDH status and exclusion of patients with IDH-mutant tumors
PRS-1 (proportion)
Months
Alkylating agents & MGMT unmethylated (n=81)
Alkylating agents & MGMT methylated (n=88)
Bevacizumab & MGMT unmethylated (n=40)
Bevacizumab & MGMT methylated (n=11)
C
PFS-1 (proportion)
Months
Alkylating agents & MGMT unmethylated (n=122)
Alkylating agents & MGMT methylated (n=138)
Bevacizumab & MGMT unmethylated (n=64)
Bevacizumab & MGMT methylated (n=20)
D
PFS-1 (proportion)
Months
Alkylating agents & MGMT unmethylated (n=81)
Alkylating agents & MGMT methylated (n=88)
Bevacizumab & MGMT unmethylated (n=40)
Bevacizumab & MGMT methylated (n=11)
E
OS (proportion)
Months
Alkylating agents & MGMT unmethylated (n=122)
Alkylating agents & MGMT methylated (n=138)
Bevacizumab & MGMT unmethylated (n=64)
Bevacizumab & MGMT methylated (n=20)
F
OS (proportion)
Months
Alkylating agents & MGMT unmethylated (n=81)
Alkylating agents & MGMT methylated (n=88)
Bevacizumab & MGMT unmethylated (n=40)
Bevacizumab & MGMT methylated (n=11)
G
Median PFS-1
Median PRS-1
6.5
8.7
Alkylating agents & MGMT unmethylated
15.0
12.2
Alkylating agents & MGMT methylated
5.6
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Bevacizumab & MGMT unmethylated
8.7
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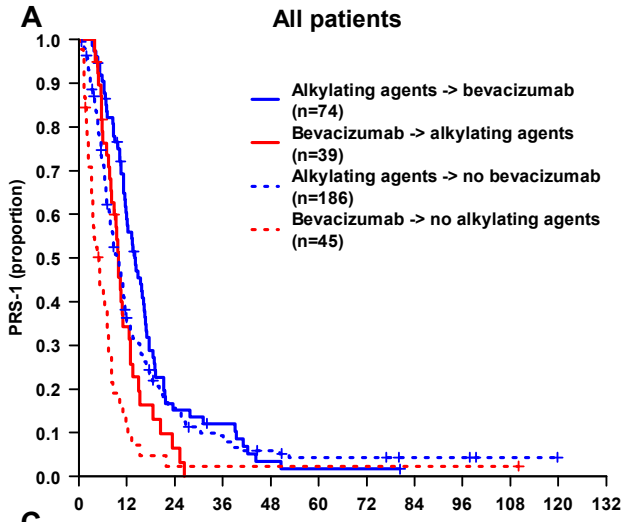
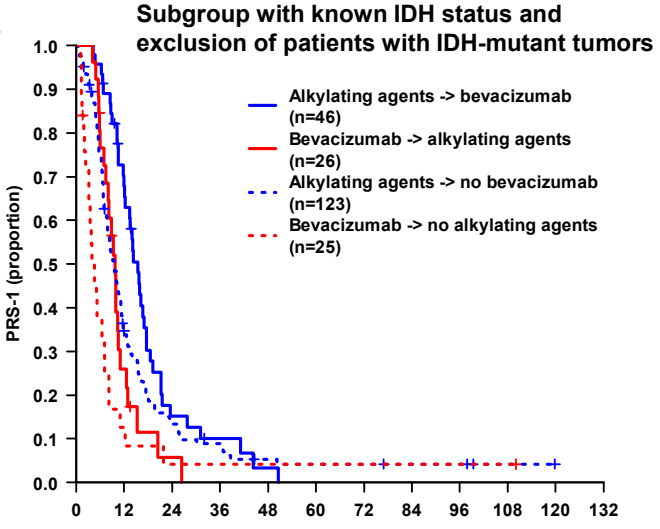
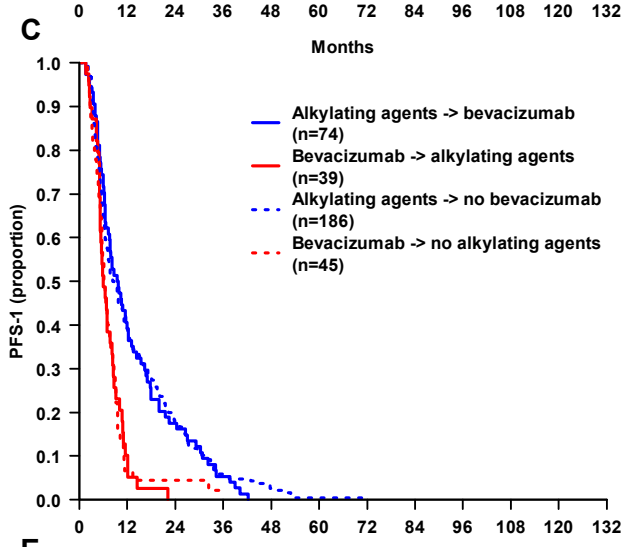
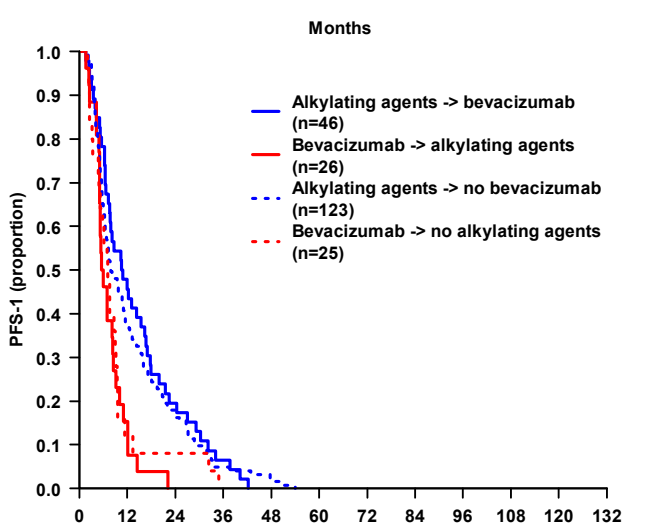
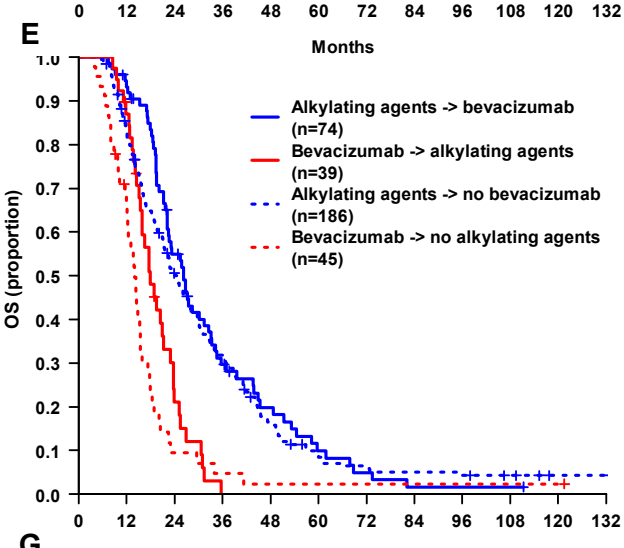
Bevacizumab & MGMT methylated
H
Median PFS-1
Median PRS-1
6.6
8.6
Alkylating agents & MGMT unmethylated
15.8
12.4
Alkylating agents & MGMT methylated
5.3
7.4
Bevacizumab & MGMT unmethylated
8.9
5.1
Bevacizumab & MGMT methylated

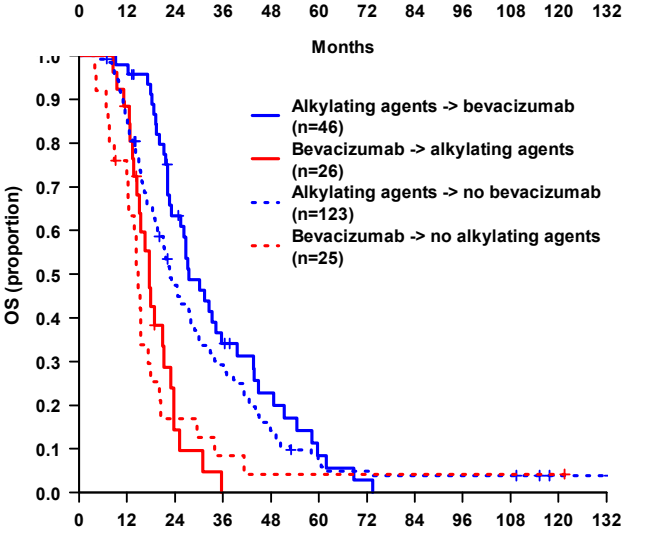

A
All patients
PRS-1 (proportion)
Alkylating agents -> bevacizumab (n=74)
Bevacizumab -> alkylating agents (n=39)
Alkylating agents -> no bevacizumab (n=186)
Bevacizumab -> no alkylating agents (n=45)
Months

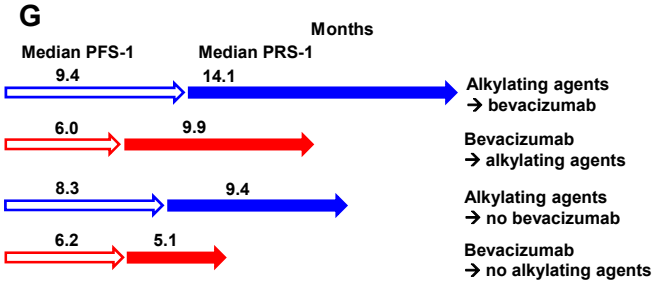

B
Subgroup with known IDH status and exclusion of patients with IDH-mutant tumors
PRS-1 (proportion)
Alkylating agents -> bevacizumab (n=46)
Bevacizumab -> alkylating agents (n=26)
Alkylating agents -> no bevacizumab (n=123)
Bevacizumab -> no alkylating agents (n=25)
Months

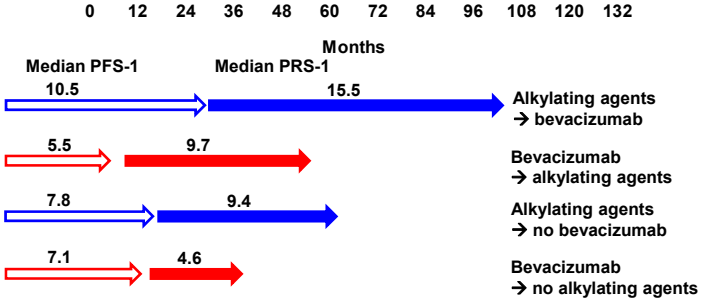

C
PFS-1 (proportion)
Alkylating agents -> bevacizumab (n=74)
Bevacizumab -> alkylating agents (n=39)
Alkylating agents -> no bevacizumab (n=186)
Bevacizumab -> no alkylating agents (n=45)
Months

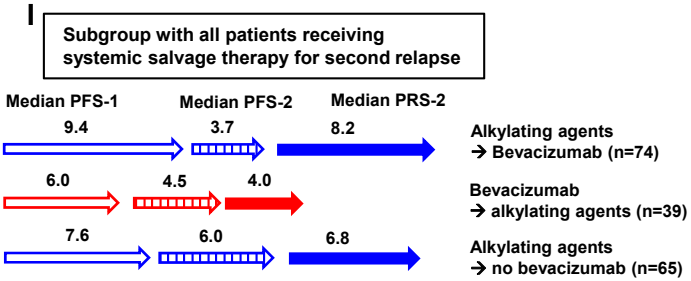

D
PFS-1 (proportion)
Alkylating agents -> bevacizumab (n=46)
Bevacizumab -> alkylating agents (n=26)
Alkylating agents -> no bevacizumab (n=123)
Bevacizumab -> no alkylating agents (n=25)
Months

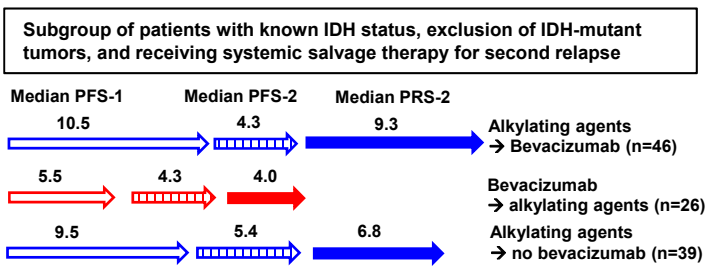

E
OS (proportion)
Alkylating agents -> bevacizumab (n=74)
Bevacizumab -> alkylating agents (n=39)
Alkylating agents -> no bevacizumab (n=186)
Bevacizumab -> no alkylating agents (n=45)
Months


F
OS (proportion)
Alkylating agents -> bevacizumab (n=46)
Bevacizumab -> alkylating agents (n=26)
Alkylating agents -> no bevacizumab (n=123)
Bevacizumab -> no alkylating agents (n=25)
Months


G
Median PFS-1
Median PRS-1
9.4
14.1
Alkylating agents → bevacizumab
6.0
9.9
Bevacizumab → alkylating agents
8.3
9.4
Alkylating agents → no bevacizumab
6.2
5.1
Bevacizumab → no alkylating agents


H
Median PFS-1
Median PRS-1
10.5
15.5
Alkylating agents → bevacizumab
5.5
9.7
Bevacizumab → alkylating agents
7.8
9.4
Alkylating agents → no bevacizumab
7.1
4.6
Bevacizumab → no alkylating agents


I
Subgroup with all patients receiving systemic salvage therapy for second relapse
Median PFS-1
Median PFS-2
Median PRS-2
9.4
3.7
8.2
Alkylating agents → Bevacizumab (n=74)
6.0
4.5
4.0
Bevacizumab → alkylating agents (n=39)
7.6
6.0
6.8
Alkylating agents → no bevacizumab (n=65)


J
Subgroup of patients with known IDH status, exclusion of IDH-mutant tumors, and receiving systemic salvage therapy for second relapse
Median PFS-1
Median PFS-2
Median PRS-2
10.5
4.3
9.3
Alkylating agents → Bevacizumab (n=46)
5.5
4.3
4.0
Bevacizumab → alkylating agents (n=26)
9.5
5.4
6.8
Alkylating agents → no bevacizumab (n=39)